REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 21, 54 and 56 have been amended. Claims 21-26, 28-29 and 52-57 are in the case and are before the Examiner.

A. The Amendments

Claim 21 was amended to more clearly recite the claimed invention by clarifying that the recited enzymes "isolated" as suggested in the Action and for which suggestion the Examiner is thanked, and that the enzymes "are present together" to emphasize the unexpected compatibility of the enzymes that are present in nature in un-isolated condition and in different cellular environments.

It is thus seen that no new matter has been added.

B. Rejection Under 35 USC §102

Claim 21 was rejected as anticipated by the disclosures of Liepkans et al. or Muramatsu et al. The Action noted that the rejection could be overcome by requiring the claimed enzymes to be "isolated". Because the claimed enzymes are often used in isolated form and without agreeing or disagreeing with the basis for rejection, the claim has been appropriately amended to speed prosecution. It is therefore believed that this basis for rejection is moot.

C. Rejections Under 35 USC §103

1. Claims 21-23, 25, 52, 54 and 56

Claims 21-23, 25, 52, 54 and 56 were rejected as allegedly obvious from the combined teachings of Bergh et al. US Patent No. 4,925,796) in view of Prieels et al., *J. Biol. Chem.* **256(20)**:10456-10463 (1981) and Schachter et al., *Methods Enzymol.* **28**:285-287 (1972). The Action notes that Bergh teaches the use of a fucosyltransferase as disclosed by Prieels and GDP-fucose to carry out a fucosylation reaction, while omitting a disclosure of a GDP-fucose forming enzymes, fucose kinase and GDP-pyrophosphorylase. The Action asserts that Schachter teaches enzymatic preparation of the GDP-fucose needed by Bergh. The action concludes that based on these disclosures, a worker of ordinary skill would have combined the enzymes and substrates to arrive at the claimed subject matter. This basis for rejection cannot be agreed with and is respectfully traversed.

The Action thus argues that each of the recited claim elements was disclosed separately in the art, and because each was known, it would have been obvious to put them together as is claimed here. On the other hand, the file of this application and its immediate predecessor contain a Declaration executed on November 08, 2004 by a pre-eminent worker in this field, Dr. James Paulson, a lead author whose work is cited in the relied-on Bergh patent. Dr. Paulson there pointed out that the enzymes involved here do not naturally occur in the same cellular compartment, nor do they act in the same cellular compartment, and that one of the enzyme products, GDP-fucose, gets transmitted back and forth between the Golgi and cytoplasm where those enzymes work in their natural environment.

The present Action attempted to refute Dr. Paulson's points by noting the Prieels paper reported isolation of what

today could be called an α1,3/4-fucosyltransferase from human milk. First, as noted in Dr. Paulson's minireview enclosed with the prior Preliminary Amendment and Reply as Exhibit 2 at page 17615 in the left column, the Golgi-attaching tail of several glycosyltransferases is cleaved, releasing the enzyme to the cytoplasm, milk and other body fluids. A similar disclosure directed specifically to an α1,3/4-fucosyltransferase is found in the right-hand column of page 11619 of Costa et al., *J. Biol. Chem.* **272(17)**:11613-11621 (1997), enclosed as Exhibit A.

The position taken in the Action thus has several flaws. First, although an active enzyme was found in human milk, no activity within the milk has been established or even asserted in the Action. That is, the fact that an active enzyme is present in milk in no way implies that that enzyme reacts with a substrate in the milk. Thus, the ability to obtain an active enzyme from human milk only illustrates that fact, an active α1,3/4-fucosyltransferase is present in and extractable from human milk.

That presence, however, teaches nothing about whether GDP-fucose is also present in human milk; whether if present, GDP-fucose is made in human milk; nor whether any activity has ever been shown between α1,3/4-fucosyltransferase, GDP-fucose made in milk and an appropriate substrate. As a consequence, the Action is back to the misplaced reliance discussed in Paragraphs 14 and 15 of Dr. Paulson's Declaration in failing to recognize the difference between mere *in vitro* enzyme activities that can be illustrated for particular enzymes and *in vivo* activity for those enzymes in making and using GDP-fucose.

Thus, one must look at all of the evidence in the record. Part of that evidence comes from a world recognized expert who stated that a skilled worker at the time the parental

application was filed would have no way to know if the enzymes and their respective substrates were compatible with each other in an *in vitro* environment until someone tried to put them together (Paulson Paragraph 16). The evidence in this record further holds that motivation for putting the enzymes together was not intuitive and there was no motivation for a worker of ordinary skill to combine the relied-on teachings as had been done (Paulson Paragraph 17).

Of course, when one looks at what was done by other workers of skill in this art prior to Dr. Wong's publications, one sees that no one put these enzymes together even though they were available. Schachter had his enzymes in 1972 and Prieels had his in 1981. Thus, it took about twenty years from the Schachter work and about ten years for Dr. Wong to do what was so blatantly obvious from the asserted motivation to combine. It is submitted that when the materials were as readily available as has been asserted, and the claimed invention was as obvious as has been asserted, someone would have done what Dr. Wong did long before he did it. The fact is no one did it.

None of the relied-on art teaches an *in vitro* system that places together an isolated glycosyltransferase and an isolated enzyme that forms a nucleoside diphosphate sugar substrate for the transferase as is here claimed. One cannot logically prove non-existence. However, the absence of facts is itself evidence that a combination of teachings that was supposed to be so facile and made with such apparent motivation but never existed in the literature was not as appropriately combined as one might have at first thought. Although seemingly simple, the workers of ordinary skill never put this invention together because they could not look backwards and say that since it was done, it was obvious to have done it. Thus, again,

the Action has improperly reconstructed the claimed subject matter through hindsight based on the teachings of the application itself, and this basis for rejection should be withdrawn.

2. Claims 21-23, 25, 52, 54 and 57

Claims 21-23, 25, 52, 54 and 57 were rejected over the Bergh, Prieels and Schachter disclosures as above, and further in view of the teachings of Demain et al. US Patent No. 4,178,210. This basis for rejection cannot be agreed with and is respectfully traversed.

The deficiencies of the tripartite Bergh, Prieels and Schachter disclosures have been discussed as they apply to the present claims. As such, adding an out of context disclosure concerning the well-known ATP regenerating system that Demain used to boost production of a cephalosporin provides nothing more to the tripartite disclosures in regard to the independent claims and therefore cannot make obvious the claims that depend from those unobvious independent claims.

Still further, as noted previously, an ATP regenerating system is not recited in the claims at issue here. Indeed, ATP is not mentioned in these claims. That is not to say that ATP cannot be present, but rather that it is not recited in the claims, nor is it needed. To rely on a disclosure that recites an ATP regenerating system to augment the Bergh or Schachter disclosures to make them operable as the Action recites that "Schachter's process requires ATP..." only underscores the inapplicability of those disclosures to these claims, and the patentability of these claims over those disclosures. The Examiner's attention is invited to Schemes 12

and 13 at pages 43 and 45 on this point. It is again submitted that this basis for rejection should be withdrawn.

3. Claims 21-26, 28, 29 and 52-57

Claims 21-26, 28, 29 and 52-57 were rejected over the Bergh, Prieels, Schachter and Demain disclosures as above further in view of the teachings of Yamamoto et al., *Agric. Biol. Chem.* **48(3)**:823-824 (1984). This basis for rejection cannot be agreed with and is respectfully traversed.

The previous discussion has illustrated the inappropriate basis for rejection provided by the combination of the Bergh, Prieels, Schachter and Demain disclosures. The addition of Yamamoto to provide the isolated disclosure of converting GDP-mannose into GDP-fucose cannot make the otherwise unobvious independent claims obvious, nor can those disclosures make obvious the claims that depend from those unobvious independent claims. It is thus submitted that this basis for rejection be with drawn.

C. Response to Arguments

The general arguments provided in the previous Reply have possibly been misunderstood, or the point trying to be made was not artfully conveyed. Regardless, the argument will be made again.

Dr. Paulson's Declaration noted that those skilled in the art at the time the first application in this series was filed were of the view that:

> 15) That because of the above-stated differences between cellular and *in vitro* manufacture of fucosylated products, the worker of ordinary skill at the time the claimed invention was made (using the first

> filing date of 1991 as that date for this paper) would have been more likely to expect interference between the enzymes, reactants and products than a lack of such interference and therefore would have required direct evidence of a lack of interference;
>
> 16) That there was no way for a worker of ordinary skill in this art to know if the enzymes and their respective substrates were compatible with each other in an *in vitro* environment until tried; (Paulson Declaration of November 08, 2004)

Dr. Paulson therefore did not state that the enzymes would not work together, nor did the Reply. Rather, he said there was a perception by skilled workers at the time, of whom Dr. Paulson was one, based on the facts stated in the preceding paragraphs of his Declaration, that the two enzymes were not compatible, and that there was no way for a worker of ordinary skill, let alone a worker of extraordinary skill such as Dr. Paulson, to know if the enzymes were compatible without doing the study.

As the Board noted in the parental application, obviousness requires a reason, suggestion or motivation to lead to a combination of teachings, and that one must also have a reasonable expectation of success in achieving the invention. It is submitted that even if one could find motivation for the combination here, Dr. Paulson's Declaration illustrates a lack of a reasonable expectation of success at the time of the filing. As such, it is again submitted that the obviousness rejections should be withdrawn.

The documents provided with the prior Reply were provided in response to the Action's request for publications to back up Dr. Paulson's position, as if his unchallenged expertise

were insufficient. Those papers did that. The aside provided by the fact that Prieels obtained his enzyme from human milk, is not relevant to the claims nor does it refute Dr. Paulson's statements as there is no evidence provided that the proper second enzyme or substrate were also present. There are a lot of useful chemicals that are extractable from bodily fluids, but that that does not mean that those chemicals are necessarily active there. One example of such chemicals are the female hormones found in pregnant mares urine that are used in Premerin®.

The Action also asserts that if product inhibition were a deterrent to motivation to combine the enzymes,

> then the artisan of ordinary skill would not have been motivated to have performed *any* enzymatic synthesis, since all enzymatic processes are subject to product inhibition. In view of the ubiquity of enzymatic processes in the prior art, applicant's argument fails from a logical standpoint, since if there were no motivation to perform enzymatic assays, on one would perform them. (Emphasis in the original.)

The quoted statement is believed to be overly broad, incorrect and is otherwise unsubstantiated. The Examiner is requested to support the quoted statement with literature references or to provide an affidavit pursuant to 37 CFR §1.104(d)(2). In addition, the claimed combination of enzymes are not used primarily in an assay, but rather in a synthetic procedure.

The Action further queries the as to why the limitation of a catalytic amount of the nucleoside-diphospho fucose forming enzyme continues to be argued. The Examiner's attention is invited to page 29, lines 28-31 wherein it is pointed out that GDP-fucose, the product of the above enzyme, can be an inhibitor of the fucosyltransferase under particular conditions. Thus, one can desire the concentration of that

enzyme to be low (a catalytic amount) so that its product will be present at a low concentration and not interfere with the subsequent reaction. Schachter, who did not have both isolated enzymes together, faced no such potential problem of too much GDP-fucose and could therefore use as much enzyme as he could muster.

The Action cites *In re McLaughlin* for the proposition that any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning. "But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the invention was made, and does not include knowledge gleaned only from the applicant's disclosure , such a reconstruction is proper." (Action at page 14.)

There is no quarrel with that statement nor with the Court's holding. The problem is that the Action did not abide by it. Thus, rather than taking into account the knowledge available at the time the invention was made, particularly that provided by Dr. Paulson who was there and working at the time, the Action has simply read the application and diverse and in some cases irrelevant disclosures, summed them and held the claimed invention to be obvious. That is the impermissible type of hindsight reconstruction.

D. Summary

Claims 21, 54 and 56 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

It is noted that Exhibits 1-7 that were provided with the previous Reply were not listed on a Form PTO-1449. A Form PTO-1449 that lists the documents new to this application from that Reply (Exhibits 1-6, Exhibit 7 having been provided previously) and Exhibit A herein are listed. Exhibit A is enclosed herewith.

A Petition for an Extension of Time and its required fee are enclosed. No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By _____

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Enclosures
- Petition and fee
- Exhibit A
- Form PTO-1449

CERTIFICATE OF MAILING

I hereby certify that this Amendment and Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop Amendments, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on September 2, 2005.

By 
Edward P. Gamson